82385_Auto_Edited.docx

WORD COUNT 1835
TIME SUBMITTED 31-MAR-2023 03:17PM
PAPER ID 98208197

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 82385
Manuscript Type: CASE REPORT

Late-onset MELAS syndrome with mitochondrial DNA 3243A>G mutation masquerading as autoimmune encephalitis: A case report

Jian-Wei Wang, Xiao-Bo Yuan, Hong-Fang Chen

Abstract

BACKGROUND

Here, we present a unique case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, which initially appeared to be autoimmune encephalitis and was ultimately confirmed as MELAS with the mitochondrial DNA 3243A>G mutation.

CASE SUMMARY

A 58-year-old female presented with acute-onset speech impediment and auditory hallucinations, symmetrical bitemporal lobe abnormalities, clinical and laboratory findings, and a lack of relevant prodromal history, which suggested diagnosis of autoimmune encephalitis. Further work-up, in conjunction with the patient's medical history, family history, and lactate peak on brain lesions on magnetic resonance imaging, suggested a mitochondrial disorder. Mitochondrial genome analysis revealed the m.3243A>G variant in the *MT-TL1* gene, which led to a diagnosis of MELAS syndrome.

CONCLUSION

This case underscores the importance of considering MELAS as a potential cause of autoimmune encephalitis even if patients are over 40 years of age and symptoms and signs are atypical for MELAS syndrome.

Key Words: MELAS; Mitochondrial DNA mutation; Encephalitis; Case report

Wang JW, Yuan XB, Chen HF. Late-onset MELAS syndrome with mitochondrial DNA 3243A>G mutation masquerading as autoimmune encephalitis: A case report. *World J Clin Cases* 2023; In press

Core Tip: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is a multimitochondrial disease caused by DNA mutations and respiratory chain defects that is frequently misdiagnosed. Here, we describe a 58-year-old patient with MELAS syndrome who initially presented with acute cognitive impairment, tinnitus, and headache and was subsequently misdiagnosed with autoimmune encephalitis. The final diagnosis was based on MELAS mutation blood tests and magnetic resonance imaging results. The patient was treated with appropriate medication and gradually improved. This case shows that MELAS syndrome should be diagnosed only after other causes, including autoimmune encephalitis, have been ruled out and the atypical clinical features of MELAS syndrome, such as older age of onset, have been considered.

INTRODUCTION

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a multisystemic mitochondrial disorder[1]. MELAS is caused by mutations in mitochondrial DNA and subsequent respiratory chain deficiency[2]. In most cases,

MELAS syndrome is characterized by severe aches, stroke-like episodes, short stature, sensorineural deafness, cognitive decline, and exercise intolerance. Conversely, hypertrophic cardiomyopathy, ataxia, ophthalmoplegia, and diabetes mellitus are rare features of MELAS[3,4]. MELAS syndrome presenting with the features of acute encephalitis is rare and has been described in only a few case reports[5,6]. Among these few cases, nonviral encephalitis is even rarer and may therefore pose a diagnostic challenge. Of note, the above clinical manifestations generally occur before the age of 40[5].

Here, we report the unique case of a 58-year-old female whose condition initially appeared to be autoimmune encephalitis and who was ultimately diagnosed with MELAS syndrome in the presence of the m.3243A>G mutation.

CASE PRESENTATION

Chief complaints

Speech impediment and auditory hallucination, accompanied by tinnitus and headache for 3 d.

History of present illness

A 58-year-old female presented with sudden cognitive dysfunction, auditory hallucinations, nonsensical behavior, inability to communicate normally with others, and complaints of headache and tinnitus. The patient had no fever, seizures, or consciousness disturbance.

History of past illness

The patient had a history of bilateral hearing loss.

Personal and family history

The patient had no history of mental retardation or cognitive decline up to the time of her acute illness. Moreover, the patient denied a family history of neuromuscular disease, encephalitis, or mitochondrial disease.

Physical examination

On admission, the patient's height was 158 cm, and her weight was 45 kg. On physical examination, her body temperature was 36.5 °C and a history of previous infection and fever were denied. Chest auscultation revealed normal respiratory sounds and a normal heart rate with no murmur. The patient's neurological examination, limited by the above symptoms, was otherwise normal.

Laboratory examinations

Routine laboratory studies, including blood glucose, hepatic and renal function, coagulation testing, glycosylated hemoglobin, autoantibodies, autoantibody spectrum associated with anti-cardiolipin antibodies, thyroid function, homocysteine, serum tumor markers, human immunodeficiency virus antibody test and syphilis spirochete hemagglutination test, were all unremarkable. The patient's serum white cell count was 14.38 × 10^9/L, and her C-reactive protein level was 7 mg/L. It is worth noting that her arterial blood lactate level was 4.7 mmol/L.

Imaging examinations

Magnetic resonance imaging (MRI) revealed high-intensity lesions in the bitemporal lobe on T2-weighted images (Figure 1A), fluid-attenuated inversion recovery (FLAIR) (Figure 1B) images, and diffusion-weighted images (DWI) (Figure 1C and E). The parts of the lesions involving the cortex appeared hyperintense on DWI (Figure 1C) and hypointense on apparent diffusion coefficient (ADC) maps (Figure 1D), features consistent with cytotoxic edema. Follow-up brain MRI obtained on Day 27 showed an extensive reduction in FLAIR/DWI signals in the left temporal lobe (Figure 1F and G), without an apparent reduction in T2 signals.

Electrophysiological detection

The electroencephalogram only indicated a slight increase in fast waves.

Further diagnostic work-up

Magnetic resonance spectroscopy also revealed a prominent doublet and elevated lactate peak with reduced N-acetyl-aspartate levels (Figure 2). Cerebrospinal fluid (CSF) showed a white cell count of 4/μL and a protein level of 0.668 g/L with a CSF pressure of 140 mmH_2O.

FINAL DIAGNOSIS

The mitochondrial DNA (mtDNA) 3243A>G mutation detected in the patient's blood led to the final diagnosis of MELAS syndrome.

TREATMENT

The patient was initially misdiagnosed with autoimmune encephalitis and treated with gamma globulin (18 mg/d × 5 d) therapy and intravenous methylprednisolone (1000 mg/d × 3 d to 500 mg/d × 3 d to 60 mg/d × 9 d). Then, the patient was discharged with slowly tapered oral methylprednisolone (44 mg/d × 2 wk followed by a dosage reduction of 4 mg every 2 wk). When the diagnosis of MELAS was confirmed by the presence of the 3243A>G mutation (Figure 3), we immediately stopped intravenous methylprednisolone and started therapy with L-carnitine (oral 1 g/d × 8 d), L-arginine (oral 4.5 g/d × 8 d), and coenzyme Q10 (oral 60 mg/d × 8 d) (Figure 4).

OUTCOME AND FOLLOW-UP

The patient gradually improved before being discharged from the hospital. At the outpatient follow-up a few months later, the patient's cognitive function had recovered well, and she was basically able to take care of herself.

DISCUSSION

Based on some classic features of MELAS syndrome, such as repeated headaches, previous history of hearing impairment, lactic acidosis, peak lactic acid on brain MRI, and the m.3243A>G mutation detected in serum, the diagnosis of MELAS was clear in our case. The clinical presentation of MELAS depends on the existence of heteroplasmy[6], which refers to the ratio of mutant to normal mtDNA, divided into four different transcription stages of 0%, 20%-30%, 50%-90%, and 100%[7]. It is generally believed that the heteroplasmy rate of typical MELAS is 50%-90%, with higher heterogeneity being associated with earlier onset time. The age of MELAS patients is mostly 10-30 years, and there are few reports of MELAS syndrome onset after 40 years of age[1,8-10]. Our patient's late age of onset and some other atypical symptoms were related to the low heteroplasmy.

This case initially appeared to be autoimmune encephalitis. Few cases of MELAS appearing as acute encephalitis have been reported[11-15]. Most of these cases appear to be herpes simplex encephalitis (HSE). Johns *et al*[11] described three cases with different onset symptoms, all of which involved 3243A>G mutations and increased serum lactic acid levels. The intracranial lesions in all three patients were located in the unilateral temporal or parietal lobes. The case reported by Sharfstein *et al*[12] was characterized by aphasia and delirium; the lesions were located in the left temporal and parietal lobes, and the patient carried the 3243A>G mutation. Hsu *et al*[13] described a patient with acute-onset pyrexia, headache, and seizures who showed aberrant pleocytosis in the CSF but no obvious abnormalities on MRI. The lesions described by both Gieraerts *et al*[14] and Caldarazzo Ienco *et al*[16] were bilateral, but in the study by Gieraerts *et al*[14], the lesions were widely distributed; in the study by Caldarazzo Ienco *et al*[16], they were confined to the bilateral temporal lobes. All of the cases in these abovementioned studies were characterized by the mitochondrial 3243A>G mutation. Of note, 80% of MELAS patients carry the m.3243A>G mutation in the MT-TL1 gene, whereas the frequency of this mutation in the general population is approximately 1:15000[17]. Diseases related to other types of mutations are also misdiagnosed as encephalitis in

approximately 20% of MELAS patients. Yokota *et al*[15] described a patient with the mtDNA 14453G→A mutation and acute cognitive impairment, psychosis, headache, and pyrexia who showed mild pleocytosis in the CSF and a lesion in the right temporoparietal lobe.

Based on the above cases, the distribution of lesions in MELAS syndrome patients can be diverse, and the symmetry of MELAS lesions is becoming gradually recognized[18,19]. However, the signal distribution of MELAS lesions on DWI and ADC is relatively unique, especially when compared with ischemic stroke lesions. MELAS lesions most often occur due to vasogenic edema; thus, the signal intensity on ADC maps is not or only mildly reduced[20,21]. In contrast, ischemic areas are primarily caused by cytotoxic edema and generally present as restricted diffusion and low signals on ADC maps[22,23]. This phenomenon is consistent with the imaging in our case.

HSE was not the first diagnosis we considered for our patient. First, the patient's CSF was normal, and the gold standard for diagnosing HSE was not detected. Second, the lesions in the bilateral temporal lobes on brain MRI reduced the likelihood of HSE[24,25], though the negative results for the presence of antibodies against neuronal surface antigens in the CSF could not rule out the possibility of autoimmune encephalitis. Graus *et al*[26] reported clinical diagnostic criteria for autoimmune encephalitis and specifically pointed out that mitochondrial diseases can result in a diagnosis different from autoimmune encephalitis. When the present patient visited one of our physicians, we accepted the original diagnosis of autoimmune encephalitis and discharged her. When she subsequently developed deteriorated mental status under normal medication, combined with the findings of magnetic resonance spectroscopy and serum lactic acid, we then considered the possibility of metabolic disorders, especially MELAS. The final diagnosis of our patient was confirmed by molecular genetic testing of mitochondrial DNA. This case highlights the importance of deferring a diagnosis of autoimmune encephalitis until alternative causes, including MELAS syndrome, have been excluded, especially in antibody-negative encephalitis. It should be recognized that some atypical clinical symptoms of MELAS, such as onset at an advanced age, and

deviation from the classic brain MRI features, including symmetry of the lesion location, are being increasingly reported. In particular, when a disease cannot be clearly diagnosed, we should decisively turn our attention to patient characteristics that do not conform to “classic” features.

CONCLUSION

This case shows that late-onset MELAS syndrome is rare but should be carefully considered in patients presenting with relevant symptoms as a crucial step in the diagnosis and treatment of such patients.

82385_Auto_Edited.docx

ORIGINALITY REPORT

17%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	87 words — 4%
2	Yuki Yokota, Makoto Hara, Takayoshi Akimoto, Tomotaka Mizoguchi, Yu-ichi Goto, Ichizo Nishino, Satoshi Kamei, Hideto Nakajima. "Late-onset MELAS syndrome with mtDNA 14453G→A mutation masquerading as an acute encephalitis: a case report", BMC Neurology, 2020 Crossref	64 words — 3%
3	T.M. Trang, P.C. Chien, B.T. Dung, N.T.H. Thu, N.T.T. Truc, V.N.C. Khang. "Adult-onset mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome with progressive sensorineural hearing loss: A case report", Radiology Case Reports, 2021 Crossref	47 words — 2%
4	Jianbo Shu, Xiufang Zhi, Jing Chen, Meifang Lei, Jie Zheng, Wenchao Sheng, Chunhua Zhang, Dong Li, Chunquan Cai. "Case Report: A Case of β-Ureidopropionase Deficiency Complicated With MELAS Syndrome Caused by Variant and Mitochondrial Gene Variant", Frontiers in Pediatrics Internet	32 words — 2%
5	Rubesh Gooriah, Badr E. A. Dafalla, Thattoli C. Venugopalan. "Led astray: MELAS initially misdiagnosed as herpes simplex encephalitis", Acta Neurologica Belgica, 2014	30 words — 2%

Crossref

6 Yoshikawa, H.. "Serial Changes on Diffusion-Weighted Magnetic Resonance Imaging in Encephalitis or Encephalopathy", Pediatric Neurology, 200604
Crossref
13 words — 1%

7 mitonet.org
Internet
12 words — 1%

8 Lv-Ping Zhuang, Chang-Yun Liu, Yuan-Xiao Li, Hua-Ping Huang, Zhang-Yu Zou. "Clinical features and genetic characteristics of hereditary diffuse leukoencephalopathy with spheroids due to CSF1R mutation: a case report and literature review", Annals of Translational Medicine, 2020
Crossref
11 words — 1%

9 Kimura, T., K. Ishizawa, T. Mitsufuji, T. Abe, Y. Nakazato, K. Yoshida, A. Sasaki, and N. Araki. "A clinicopathological and genetic study of sporadic diffuse leukoencephalopathy with spheroids: A report of two cases", Neuropathology and Applied Neurobiology, 2013.
Crossref
10 words — 1%

10 theroyalacademybd.com
Internet
10 words — 1%

11 worldwidescience.org
Internet
10 words — 1%

12 www.wjgnet.com
Internet
10 words — 1%